# CYCLIZATION OF THE ENE REACTION PRODUCTS FROM HEXAFLUOROACETONE IMINE: SYNTHESIS OF BIS(TRIFLUOROMETHYL)PYRROLIDINE DERIVATIVES[1]

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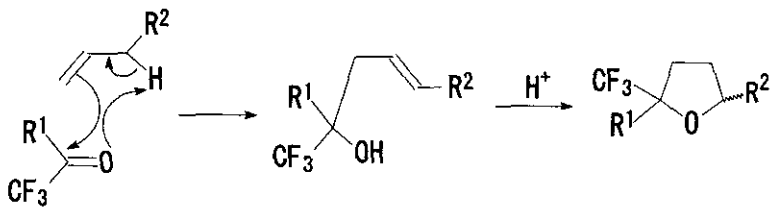
***This paper is dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday.***

**Abstract** -- *N*-Tosylhexafluoroacetone imine reacted as a good enophile with ene components to give α,α-bis(trifluoromethyl)homoallylamine derivatives. Cyclization of the ene reaction products in the presence of *p*-toluenesulfonic acid gave α,α-bis(trifluoromethyl)pyrrolidine derivatives, when the δ position of the homoallylamino group was substituted with an aromatic ring, while no reaction occurred, when substituted with an alkyl group.

We have developed the ene reaction of trifluoromethyl carbonyl compounds and reported its application for the synthesis of various trifluoromethyl compounds.[2] Among these applications, α-(trifluoromethyl)homoallyl alcohols, the products of the ene reaction, were readily converted to trifluoro- methylated tetrahydrofuran derivatives by treatment with *p*-toluenesulfonic acid in boiling benzene,[3] as shown in Scheme 1.

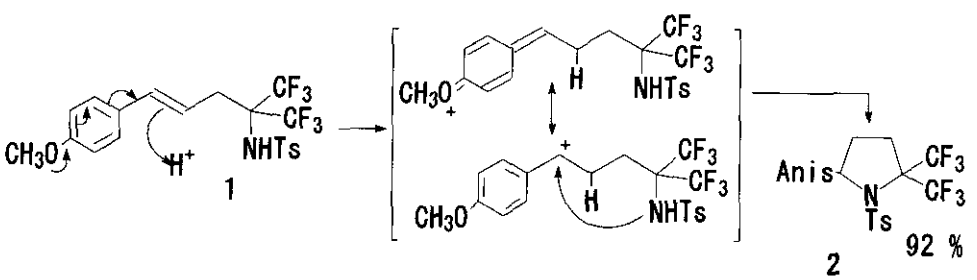
*Scheme 1*



Further, we found that *N*-tosylhexafluoroacetone imine reacted as an enophile with ene components having a terminal vinyl group.[4] Now, we would like to report cyclization of the ene reaction products of the imine to trifluoromethylated pyrrolidines

When the ene reaction product (**1**) from the imine and 4-allylanisole was heated in the presence of *p*-toluenesulfonic acid in xylene, it cyclized to 5-(4-anisyl)-1-(*p*-toluenesulfonyl)-2,2-bis(trifluoromethyl)pyrrolidine (**2**) in a quantitative yield. The mechanism of this cyclization was speculated as shown in Scheme 2.

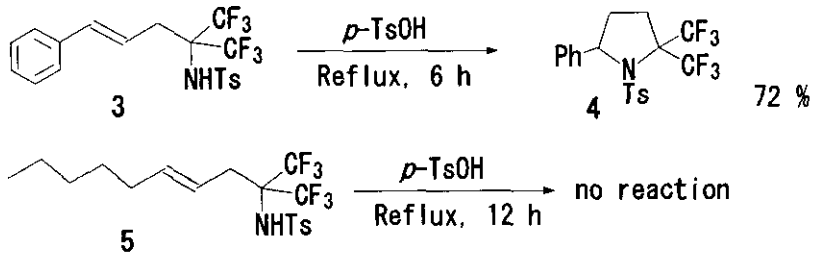
*Scheme 2*



Thus, at first protonation occurs at the β-position from the benzene ring, then the lone pair on the nitrogen the benzylic cation attacks the quinone methide cation to give the cyclization product.

To assess the scope of this reaction, we examined the similar reaction of the ene reaction products (**3**, and **5**) from allylbenzene and 1-octene. Compound (**3**) cyclized similarly to give the corresponding pyrrolidine (**4**), but **5** did not cyclize at all even by a prolonged reaction time (see Scheme 3).

*Scheme 3*




These results support the mechanism mentioned above. Namely, formation of the benzylic cation by protonation is the key step of this cyclization Compound (**5**) could not form a reactive quinone methide intermediate and did not cyclize.

*In conclusion, trifluoromethylated pyrrolidine derivatives were obtained using the ene reaction of* hexafluoroacetone imine. Stabilization of the intermediate cation by an adjacent benzene ring is indispensable for this reaction. Ene reaction of other trifluoromethylated imines is in progress.

## EXPERIMENTAL

**General** -- Melting points were measured on Micro Melting Point Apparatus, Model MP, Yanagimoto, Kyoto, Japan, and Melting Point Apparatus, Ishii Shoten, Tokyo, Japan, and uncorrected. $^1$H-Nmr spectra were *recorded on a* JEOL-FX90Q and a JNM-GX400 spectrometers $^{19}$F-Nmr spectra were measured on a Hitachi R-1500 spectrometer Benzotrifluoride (BTF) was used as an internal standard. The upper field was shown as plus.

**Cyclization of 1** -- A solution of **1** (0.60 g, 1.3 mmol) and *p*-TsOH·$H_2O$ (0.25 g, 1.3 mmol) *in xylene (10 ml)* was refluxed for 6 h. After the mixture was cooled, the precipitates were collected by filtration, and washed with $CH_2Cl_2$. The mother liquor and the washings were combined and concentrated under vacuum. The residue was separated by column chromatography ($SiO_2$, hexane - $CH_2Cl_2$, 2:1 to 0.1). The main fraction and the precipitates were combined and recrystallized from $CH_2Cl_2$ to give **2** (0.55 g, 92 %) Colorless plates, mp

125-126°C, ms *m/z* 467 ($M^+$) High resolution ms Calcd for $C_{20}H_{19}NO_3F_6S$: 467.088. Found. 467.088, $^1$H-nmr ($CDCl_3$) δ:1.90-2.00 (1H, m), 2.22-2.35 (1H, m), 2.30 (3H, s), 2 45-2.64 (2H, m), 3.72 (3H, s), 4.98 (1H, dd, J=7.9, 7.6 Hz), 6.51 (2H, d, J=8.9 Hz), 6.90 (2H, d, J=8.9 Hz), 6.92 (2H, d, J=8.2 Hz), 7.12 (2H, d, J=8 2 Hz), $^{19}$F-nmr ($CDCl_3$) ppm : -3.18 (3F, q, J=8 0 Hz), -8.35 (3F, q, J=8.0 Hz).

**Cyclization of 3** -- A similar reaction of **3** for 6 h gave **4** in the yield of 72 %. **4**. Colorless plates, mp 132-133°C ($CH_2Cl_2$), ms *m/z*. 437 ($M^+$). High resolution ms Calcd for $C_{19}H_{17}NO_2F_6S$: 437.088. Found: 437 088, $^1$H-nmr ($CDCl_3$) δ: 1.90-2.00 (1H, m), 2.25-2.44 (1H, m), 2.29 (3H, s), 2.51-2.66 (2H, m), 5 05 (1H, dd, J=7 6, 7.6 Hz), 6.90 (2H, d, J=8.3 Hz), 6 98-7.03 (5H, m), 7 19 (2H, d, J=8.3 Hz), $^{19}$F-nmr ($CDCl_3$) ppm: -3.15 (3F, q, J=8 8 Hz), -8.32 (3F, q, J=8.8 Hz).

## REFERENCES AND NOTES

1. This work was reported in the 113th Annual Meeting of Pharmaceutical Society of Japan, Osaka, March, 1993.

2. Review: I. Kumadaki, *Reviews on Heteroatom Chemistry*, 1993, **9**, 181.

3. T. Nagai, T. Miki, and I Kumadaki, *Chem. Pharm. Bull.*, 1987, **35**, 3260.

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